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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KAMERON W. MAXWELL and PETER C. HOYLE

Appeal[1] 2008-5692
Application 10/675,225
Technology Center 1600

Decided:[2] April 16, 2009

Before DEMETRA J. MILLS, LORA M. GREEN, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1] The Oral Hearing scheduled for March 19, 2009, was waived.

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-17 and 19-25. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a pharmaceutical composition for use in ameliorating an effect of radiotherapy on skin. Claims 1, 13 and 24 are representative of the claims on appeal, and read as follows:

1. A pharmaceutical composition for use in ameliorating an effect of radiotherapy on skin, mucous membranes, or hair follicles, comprising:
a solvent; and
an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel.

13. A pharmaceutical composition for use in ameliorating an effect of radiotherapy to skin or mucous membranes, comprising:
a solvent; and
an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel or low-residue thickened liquid that does not leave an amount of residue sufficient to enhance burning to the skin or mucous membranes when radiotherapy is applied.

24. A method of treating a patient, comprising:
topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent;
evaporating solvent; and
applying radiotherapy to said patient.

The Examiner relies on the following evidence:

Mitchell	US 5,462,946	Oct. 31, 1995
Golz-Berner	US 6,426,080 B1	Jul. 30, 2002

We affirm-in-part.

ISSUE

The Examiner finds that claims 1, 2, 6-10, 12-18, and 20-25 are anticipated by Mitchell.

Appellants contend that Mitchell does not disclose, either explicitly or inherently, a low-residue gel or thickened liquid formulation as required by the claims; and as to claim 24, Appellants contend that Mitchell does not disclose the timing of the topical formulations with respect to the application of ionizing radiation.

Thus, the issue on appeal is: Has the Examiner established by a preponderance of the evidence that Mitchell explicitly or inherently discloses a low-residue gel or thickened liquid formulation as required by the claims; or that Mitchell, either explicitly or inherently, anticipates the method of claim 24?

FINDINGS OF FACT

FF1 According to the Specification, the "invention relate[s] to pharmaceutical compositions for use in ameliorating an effect of radiotherapy on skin, mucous membranes, or hair follicles including a solvent and an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, preferably a solvent that is thickened or is in the form of a low-residue gel." (Spec. 3, ¶10.)

FF2 The Specification notes that others, such as Mitchell, have "suggested the use of Tempol, a stable nitroxide radical . . . as a topical formulation to ameliorate the effects of radiotherapy," but "limit the topical use of Tempol to formulations selected from creams, lotions, shampoos, cream rinses, and ointments." (*Id.* at 2, ¶9.) The Specification further notes that "[i]t is now recognized that these kinds of topical formulations are unsuitable for administration shortly before the actual therapy of radiotherapy to the patient" as those "product forms leave residues that can result in topical burning, including severe burns, when radiation is administered." (*Id.*)

FF3 The solvents that may be used in the pharmaceutical compositions of the invention include water, urea, alcohols, and glycols (*id.* at 3, ¶11). The pharmaceutical composition may be thickened "with a viscosity-enhancing agent, such as carboxymethylcellulose, a gum such as guar gum, an alginate, or other low-residue thickening agent, or is in the form of a low-residue gel." (*Id.* at 4, ¶16.)

FF4 According to the Specification, in addition to the nitroxide protector and the solvent, the topical compositions may also include:

> [P]olymers, colorants, antimicrobials, preservatives, antioxidants, alcohols, emollients, additional active ingredients, ingredients that enhance the permeability of the treated area, water, and other ingredients commonly used in low-residue topical formulations. Additional ingredients in the compositions herein are acceptable as long as the formulation, as a whole, remains low residue.

(*Id.* at 19, ¶80.)

FF5 The Specification defines a gel as "a semisolid system of either suspensions made up of small inorganic particles or large organic molecules

interpenetrated by a liquid." (*Id.* at 20, ¶91.) According to the Specification, gels, if left undisturbed for some time, may be in a semisolid or gelatinous state, and that small amounts of water may separate on standing (*id.*).

FF6 The Specification teaches:

> A gel according to the present invention will typically comprise a major amount of a liquid phase and a minor amount of a thickening or gelling agent. The gelling agent, in preferred embodiments, will comprise only 5%, 4%, 3%, 2%, 1%, 0.5% or less of the total volume or weight of the composition; thus, when applied to the skin or mucosa, the liquid can evaporate, leaving only the gelling agent and the active ingredient. In this manner, 98%, 99%, or more of the carrier for the drug can disappear prior to radiotherapy, greatly reducing or eliminating topical burning due to the bolus effect.

(*Id.* at 14, ¶64.)

FF7 The Specification also defines "low-residue" as "formulations that can be applied to a patient, shortly before undergoing radiotherapy, without leaving a residue capable of enhancing a bolus effect upon delivering radiotherapy to the treated area." (*Id.* at 18, ¶77.) A bolus effect is "burning caused by the residue or film." (*Id.* at 15, ¶68.)

FF8 The Specification teaches that the gel may be prepared "by slowly dispersing one or more suitable polymers in the requisite amount of suitable solvents." (*Id.* at 20-21, ¶92.)

FF9 The Specification exemplifies formulations containing TEMPO, ethanol, water, and Klucel or Laponite XLG (*see id.* at 24, Example 1; *id.* at 29, Example 2).

FF10 The Examiner rejects claims 1, 2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being anticipated by Mitchell (Ans. 3).

FF11 The Examiner finds that Mitchell teaches pharmaceutical compositions and methods of using the composition, wherein "the compositions contain nitroxide compounds (including TEMPOL) that can be used as radiation protectants for skin, mucositous and hair loss (also known as alopecia), which can be applied as an ointment, lotion, or cream (satisfying the claim for a gel or thickened liquid)." (*Id.* (citing Mitchell, col. 1, ll. 10-13; col. 2, ll. 53-58; and claims 1 and 10.)

FF12 The Examiner acknowledges that the "patent is silent on specific solvents," but finds that "it is deemed inherent by the examiner that in order to make a topical cream or lotion the active ingredient would have to be dissolved in some type of solvent and the patent describes the compounds having concentrations of from 1-5 mM and the use of acceptable carriers." (Ans. 3 (citing Mitchell, col. 4, ll. 40-51).)

FF13 The Examiner finds that "since Mitchell teaches all of appellants claimed ingredients the properties of the composition would be the same." (Ans. 7.)

FF14 The Examiner also finds that "'low-residue' is a relative term and as such it is unclear how limiting the recitation is in regards to the amount of residue that can be present for a composition to still read on appellant's claimed invention." (*Id.*)

FF15 Mitchell discloses "pharmaceutical compositions containing nitroxide compounds useful in ameliorating the deleterious effects of toxic oxygen-

related species in living organisms, and methods of using the same."

(Mitchell, col. 1, ll. 10-13.)

FF16 Mitchell discloses:

> Ionizing radiation protectants to protect skin, and to protect against mucositis, the effects of whole body radiation, and radiation-induced hair loss. Administration in these situations may be accomplished either via topical application as an ointment, lotion, or cream, intravenously or orally by pill or lozenge.

(*Id.* at col. 2, ll. 53-59.)

FF17 Mitchell states that "[i]t is contemplated that the invention compounds will be formulated into pharmaceutical compositions comprising an effective antioxidant amount of [nitroxides] and pharmaceutically acceptable carriers." (*Id.* at col. 4, ll. 47-51.) According to Mitchell:

> These pharmaceutical compositions may take the form of a solution, emulsion, suspension, ointment, cream, aerosol, granule, powder, drops, spray, tablet, capsule, sachet, lozenge, ampoule, pessary, or suppository. They may be administered parenterally, intramuscularly or subcutaneously, intravenously, intra-articularly, transdermally, orally, buccally, as a suppository or pessary, topically, as an aerosol spray, or drops.

(*Id.* at col. 5, ll. 7-13.)

FF18 Mitchell does not exemplify any topical compositions comprising a nitroxide.

PRINCIPLES OF LAW

"It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art

reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). Under the principle of inherency, when the prior art reference is silent as to the limitation asserted to be inherent, it need be clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by the ordinary artisan. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Id. at 1269 (quoting *In re Oelich*, 666 F.2d 578, 581 (CCPA 1981)).

ANALYSIS

Appellants argue that the Specification specifically defines "low-residue" (FF7), and that Mitchell does not disclose a low-residue formulation (*id.* at 8-9). Appellants assert further that the Specification teaches (FF2) that prior art creams, lotions, etc, such as those taught by Mitchell, leave a residue on the skin that can result in severe burning when applied shortly before undergoing radiotherapy (App. Br. 8).

Appellants argue further that Mitchell does not disclose a "'thickened liquid'" or "'gel'" formulation (*id.* at 5). Appellants argue that the Specification provides a definition for a gel (FF5), and teaches how a

thickened liquid may be obtained (FF6, FF8), as well as distinguishes between gels and thickened liquid formulation and other formulations such as creams, lotions, shampoos, cream rinses, and ointments of the prior art (FF2), and that Mitchell does not meet this limitation (App. Br. 6-8).

We have carefully considered the rejection made by the Examiner, and the arguments of Appellants, and conclude that Appellants have the better position. The Specification defined "low-residue" as "'formulations that can be applied to a patient, shortly before undergoing radiotherapy, without leaving a residue capable of enhancing a bolus effect upon delivering radiotherapy to the treated area.'" (FF7.) The Specification also notes that the low-residue gels only contain a minor amount of thickening or gelling agent, such as 5% or less (FF6).

Mitchell does not exemplify any topical preparations containing a nitroxide (FF18), and does not teach or suggest the need of having a low-residue gel or thickened liquid to prevent burning caused by a residue or film of the topical preparation. As inherency may not be established by probabilities or possibilities, the Examiner has not established by a preponderance of the evidence that Mitchell inherently discloses a low-residue gel or thickened liquid. As independent claims 1, 13, 15, 16, and 25 all require a low-residue gel or thickened liquid, the Examiner has not established that Mitchell anticipates those claims.

As to claim 24, Appellants argue that in order to anticipate the claim, evaporation of the solvent must occur before radiotherapy is applied to the patient, and "Mitchell does not disclose the timing of the application of the

topical formulations with respect to the application of ionizing radiation." (App. Br. 11.)

Claim 24 stands on a different footing than the remainder of the independent claims. Claim 24 does not require a low-residue gel or low-residue thickened liquid. Rather, claim 24 requires the steps of: 1) topically applying a sufficient amount of a nitroxide protector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent; 2) evaporating solvent; and 3) applying radiotherapy to said patient. The only step that is in contention is step 2, evaporating the solvent.

Giving the claim language its broadest reasonable interpretation, the limitation of "evaporating the solvent" reads on any amount of solvent being evaporated. *See In re American Academy Of Science Tech Center*, 367 F.3d 1359, 1363 (Fed. Cir. 2004) (noting that during prosecution before the Office, claims are to be given their broadest reasonable interpretation consistent with the Specification as it would be interpreted by one of ordinary skill in the art). Mitchell teaches applying a topical preparation, such as an ointment, cream, or lotion, to protect skin against the effects of whole body radiation (FF16). The ordinary artisan would understand that as the topical preparation is applied, at least a small part of the solvent would necessarily evaporate, such that the ointment or cream remains on the skin where it is applied. Thus, we find that Mitchell inherently anticipates the method of claim 24.

CONCLUSION(S) OF LAW

We find that the Examiner has not established by a preponderance of the evidence that Mitchell explicitly or inherently discloses a low-residue gel or thickened liquid formulation as required by independent claims 1, 13, 15, 16, and 25. We do find, however, that Mitchell inherently anticipates the method of claim 24.

We thus reverse the rejection of 1, 2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being anticipated by Mitchell as to claims 1, 2, 6-10, 12-18, 20-23, and 25, but affirm as to claim 24.

ISSUE

The Examiner concludes that claims 1-17 and 19-25 are rendered obvious by the combination of Mitchell and Golz-Berner.

Appellants contend that one of skill would not produce a "low-residue" formulation even by combining the teachings of Mitchell and Golz-Berner, as neither reference teaches or suggests a low-residue dosage form.

Thus, the issue on appeal is: Has the Examiner established by a preponderance of the evidence that the combination of Mitchell and Golz-Berner teaches or suggests a low-residue dosage form of a nitroxide radioprotector?

FINDINGS OF FACT

FF19 The Examiner rejects claims 1-17 and 19-25 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Mitchell and Golz-Berner (Ans. 4).

FF20 Mitchell is relied upon as for the anticipation rejection (*id.*).

FF21 The Examiner relies on Golz-Berner for teaching "a cosmetic preparation of active substances to protect the skin (including TEMPOL) in the form of a gel composed of hydrogels (including natural polymers such as hydroxymethylcellulose), solvent (including ethanol) and other ingredients such as carriers (propylene glycol and water are listed)." (*Id.* (citing Golz-Berner, col. 3, ll. 23-29; col. 6, ll. 6-9, col. 7, l. 3; col. 7, ll. 60-62; col. 9, l. 13 and ll. 37-40).)

FF22 Golz-Berner discloses a "cosmetic preparation of active substances protects the skin in a particularly effective way against free radical aggression, both alone and in combination with other active substances." (Golz-Berner, col. 1, ll. 5-8). The preparation "keeps its radical protection potential over a long period of time." (*Id.* at col. 1, ll. 52-54.)

FF23 The cosmetic preparation of Golz-Berner

> consists of a Quebraco blanco bark extract containing at least 90 wt. % proanthocyanidin oligomers, a silkworm extract containing the peptide cecropin, amino acids and a vitamin mixture, a non-ionic, cationic or anionic hydrogel, phospholipids and water, and may also contain further active substances such as vitamin derivatives and plant extracts of acerola, sea weed, citrus, bitter orange, cherry, papaya, tea, coffee beans, Mimosa tenuiflora and angelica.

(*Id.* at Abstract.)

FF24 Golz-Berner teaches that:

> The radical protection factor (RPF) determines the activity of a substance for binding free radicals as compared with a test substance. The test substance consists of a highly reactive, semi-stable radical, which reacts with all known antioxidants. Such radicals include nitroxides such as proxo (2,2,5,5-tetramethyle-l-dihydropyrrolinoxy-nitroxide), tempol (2,2,6,6-tetramethyl-1-piperidinoxy-4-ol-nitroxide), DTBN (ditert-butyl-nitroxide) or preferably DPPH (1,1-diphenyl-2-picryl-hydrazyl).

(*Id.* at col. 7, ll. 56-63.)

FF25 The Examiner concludes:

> It would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to combine the art described in the documents above because Mitchell discloses all of the claimed invention by the appellants except the exact solvents and polymers used while Golz-Berner discloses a cosmetic preparation of active substances to protect the skin including TEMPOL and discloses the use of solvents, carriers and hydrogels which are the same as the appellant's claimed ingredients (ethanol, propylene glycol, water and natural polymers). One of ordinary skill in the art would have a reasonable expectation of success in combining the references above because they are both related to the same general field of endeavor, namely topical compositions comprised of TEMPOL for protection from harmful free radicals. Thus the claimed invention would have been *prima facie* obvious since all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

(Ans. 4-5.)

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

ANALYSIS

We summarily affirm the rejection as to claim 24 as, for the reasons set forth above, we have already found that claim 24 is anticipated by Mitchell, and "'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002).

As to the remainder of the claims, according to Appellants, the "topical formulations of the present application are designed to leave little residue on the skin after a short period of time, in order to ameliorate or avoid the problem of burning caused by radiotherapy." (App. Br. 12.)

Appellants argue that "[o]ne of skill in the art would not produce a 'low-residue' formulation even by combining the teachings of Mitchell and Golz-Berner," as neither reference teaches or suggests a low-residue dosage form (*id.*; *see also* Reply Br. 9). Appellants assert that the cosmetic preparations of Golz-Berner are designed to keep their radical protection over a long period and include phospholipids, that would not readily evaporate and leave a residue that would cause topical burning during radiotherapy (App. Br. 13). Appellants argue further that the Examiner has isolated the teachings of a hydrogel and a nitroxide from Golz-Berner, and ignores the remainder of the ingredients in the cosmetic preparation (Reply Br. 9).

Again, we conclude that Appellants have the better position. As noted by Appellants, Golz-Berner teaches a cosmetic preparation having multiple components (FF23), wherein the preparation keeps its radical protection potential over a long period of time (FF22). Thus, the Examiner has not established by a preponderance of the evidence that adding a nitroxide radioprotector to the cosmetic preparation of Golz-Berner would result in a low-residue dosage form in view of the teaching of Golz-Berner that the preparation keeps its radical protection potential over a long period of time, and the fact that neither Mitchell nor Golz-Berner recognizes the need for a low-residue dosage form.

CONCLUSIONS OF LAW

We thus conclude that the Examiner has not established by a preponderance of the evidence that the combination of Mitchell and Golz-

Berner teaches or suggests a low-residue dosage form of a nitroxide radioprotector.

We thus reverse the rejection of claims 1-17 and 19-25 under 35 U.S.C. § 103(a) as being obvious over the combination of Mitchell and Golz-Berner as to claims 1-17, 19-23, and 25, but affirm as to claim 24.

SUMMARY

We reverse the rejection of 1, 2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being anticipated by Mitchell as to claims 1, 2, 6-10, 12-18, 20-23, and 25, but affirm as to claim 24.

In addition, we reverse the rejection of claims 1-17 and 19-25 under 35 U.S.C. § 103(a) as being obvious over the combination of Mitchell and Golz-Berner as to claims 1-17, 19-23, and 25, but affirm as to claim 24.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc

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